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Review

Advances in nanomedicine for the management of uterine fibroids: From preclinical evidence to clinical challenges

Kosar Amiri Andi [1], Fatemeh Tohidi [2, *], Ali Taravati [3]

[1] Student Research Committee, Babol University of Medical Sciences, Babol, Iran
[2] Cellular and Molecular Biology Research Center, Health Research Institute, Babol University of Medical Sciences, Babol, Iran
[3] Department of Molecular and Cell Biology, Faculty of Basic Sciences, University of Mazandaran, Babolsar, Iran.

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Abstract

Background: Uterine fibroids are the most common benign tumors in women of reproductive age, often causing bleeding, pain, infertility, and reduced quality of life. Conventional therapies are limited by systemic toxicity, recurrence, and surgical morbidity. Nanotechnology offers a transformative avenue for uterus-sparing, targeted treatment.

Methods: This narrative review synthesizes preclinical and early clinical evidence on nanomedicine strategies for uterine fibroids, including polymeric and lipid-based drug carriers, gene/RNA delivery systems, theranostic nanoparticles, and extracellular matrix (ECM)-modulating approaches. Studies were assessed for therapeutic efficacy, delivery optimization, safety, and translational potential.

Results: Nanoformulations enhance drug solubility, stability, and controlled release, increasing local accumulation and anti-fibroid effects. Polymeric and liposomal platforms, SPION-based carriers, and gene/RNA nanotherapies effectively reduced fibroid volume, inhibited proliferation, and induced apoptosis in preclinical models. ECM-targeted injections improved tissue penetration and elasticity, while combination with high-intensity focused ultrasound (HIFU) further amplified therapeutic precision and minimized systemic exposure. Despite these advances, clinical translation is constrained by limited human trials, fibroid heterogeneity, dense ECM barriers, and insufficient long-term safety and fertility data.

Conclusion: Nanomedicine provides a versatile, minimally invasive platform for targeted, uterus-preserving fibroid therapy. Future research should prioritize early-phase clinical trials, optimized nanoparticle design, comprehensive safety and pharmacokinetic evaluation, and fertility-centered outcomes. By reducing surgical burden and enhancing precision, nanotechnology holds the potential to redefine fibroid management and improve quality of life for women seeking fertility-sparing treatments.

Keywords: Drug Carriers, Infertility, Leiomyoma, Nanomedicine, Precision Medicine, Quality of Life,

Introduction

Uterine fibroids (UF), also referred to as leiomyomas or myomas, are the most common benign tumors in the female pelvis. Historical evidence indicates that UF has been present since ancient times, with findings in Egyptian mummies and other archaeological remains (1). Hippocrates referred to these lesions as the "stones of the uterus," while Galen called them scleroma (2).

Later, Rokitansky proposed the term fibroma in 1860, and Virchow suggested myoma (3).

UF originates from uterine smooth muscle cells and fibroblasts and can affect over 70% of women from reproductive age until menopause (4). Stem-like cells, which constitute approximately 1% of the tumor, are considered pivotal in disease initiation and progression (2, 5). Clinically, fibroids vary in number, size, and location, with giant fibroids weighing over 11 kg

***Correspondence author:** Dr. Fatemeh Tohidi, Cellular and Molecular Biology Research Center, Health Research Institute, Babol University of Medical Sciences, Babol, Iran, **Tel:** +981132199592, **Email:** tohidi187@yahoo.com

reported in some cases (3, 6). Fibroid growth is largely driven by excessive extracellular matrix (ECM) deposition, which contributes to tissue rigidity and persistence (7, 8).

Common clinical manifestations include an enlarged uterus, abdominal pain, urinary and gastrointestinal symptoms, dyspareunia, and abnormal uterine bleeding leading to anemia (9, 10). Fibroids are also associated with infertility, recurrent miscarriage, low implantation rates, and obstetric complications such as preterm delivery, membrane rupture, placental abruption, and postpartum hemorrhage (11-15).

Current treatment guidelines include surgery, pharmacotherapy, and minimally invasive procedures, which are often limited by side effects, disease recurrence, and, in the case of hormonal therapies, reduced bone mineral density (15-18). Conventional drug therapy is frequently constrained by high dosage requirements, reduced compliance, and limited effectiveness.

Recent advances in nanotechnology offer promising alternatives. Nano-based systems improve drug bioavailability, prolong circulation time, enable controlled release, and allow targeted delivery to fibroid tissue, minimizing systemic toxicity (19, 20). Hydrogel-based systems, such as chitosan hydrogels, have also been investigated for bioactive compound delivery and controlled drug release (19, 21-23). Nanocarriers, in particular, offer the ability to retain therapeutic agents at the target site, enhance tissue-specific concentration, and prevent premature drug degradation (21, 24).

Despite these advancements, most evidence remains preclinical, derived from in vitro or animal studies, with limited high-quality clinical trial data (20, 25). The pathological role of ECM accumulation and fibroblast activation in UF underscores the potential of targeted nanotherapy, particularly for anti-fibrotic strategies that modulate ECM remodeling and fibroblast activity (26-30).

This review focuses on nanotechnology-based therapies for UF, summarizing drug nanocarriers, gene/RNA delivery systems, theranostic/magnetic strategies, and ECM-targeting modalities, and evaluates the quality of evidence, clinical translatability, and future directions.

Materials & Methods

A comprehensive literature review was conducted to synthesize preclinical and clinical evidence on nanomedicine applications in uterine fibroid management. Studies investigating polymeric, lipid-based, metallic/magnetic, gene/RNA-based, and ECM-targeting nanoparticles were included. Evidence from in vitro experiments, animal models, patient-derived xenografts (PDX), and human studies were assessed.
Key databases were searched for publications on:

1. Polymeric and lipid nanocarriers for drug delivery, including 2-methoxyestradiol (2-ME) and simvastatin.
2. Gene and RNA delivery systems using nanoparticles, including peptide polyplexes, SPIONs, and RNA-LNPs.
3. Theranostic and magnetic nanoparticles for drug delivery and imaging.
4. ECM-modulating strategies, including injectable nanogels and enzyme-based local treatments.

Inclusion criteria encompassed studies reporting efficacy, pharmacokinetics, safety, and translational potential. Articles on hybrid therapies combining nanocarriers with HIFU, uterine artery embolization (UAE), or surgical approaches were also included.

Results

The review of nanotherapeutic strategies for uterine fibroids reveals a diverse array of preclinical and early clinical findings demonstrating both the potential and limitations of these approaches. Polymeric nanosystems, particularly those based on PEG-PLGA nanoparticles, have shown significant efficacy in preclinical models. For example, 2-methoxyestradiol (2-ME) encapsulated in PEG-PLGA nanoparticles achieved high encapsulation efficiency (~99%), uniform release profiles, and prolonged systemic stability. In patient-derived xenograft (PDX) models, this nanosystem reduced tumor volume by approximately 51% over 28 days, while significantly decreasing Ki-67 expression, a marker of cellular proliferation, and showing minimal systemic toxicity (31). These findings indicate that polymeric nanoparticles can overcome pharmacokinetic limitations such as low solubility and rapid metabolism of free drugs, enabling more effective and uterus-sparing therapy.

Liposomal and lipid-based nanosystems also demonstrated promising preclinical results. Nanoliposomes loaded with 2-ME in a human uterine fibroid xenograft model reduced tumor volume by 30.5%, decreased Ki-67 expression by 55.8%, and

increased cleaved caspase-3 levels by 67.5%, with no significant systemic toxicity (32). Simvastatin-loaded liposomal nanoparticles were also evaluated in a patient-derived xenograft model; the formulation was well tolerated, although tumor growth reduction did not reach statistical significance, suggesting the need for further dose optimization (33). Other lipid-based agents, such as EGCG-loaded nanoliposomes and Labisia pumila extracts, showed anti-proliferative and pro-apoptotic effects in fibroid cells, though their in vivo efficacy remains underexplored (34, 35). These studies highlight the versatility of liposomal systems in delivering both hydrophilic and hydrophobic agents with improved stability and tissue-targeted release.

Table 1. Preclinical nanoplatforms evaluated for uterine fibroid therapy: compounds, study models, and key therapeutic outcomes

System/formulation	Drug/compound	Study model	Key outcome	Evidence level	Reference
PEG–PLGA nanoparticles	2-Methoxyestradiol (2-ME)	Patient-derived xenograft (PDX), 28-day treatment	~51% reduction in tumor volume; decreased Ki-67; no notable systemic toxicity	Strong / high credibility (PDX)	(31)
Nanoliposomes	2-Methoxyestradiol (2-ME)	Human uterine fibroid xenograft model	30.5% reduction in tumor volume; decreased Ki-67; increased cleaved caspase-3; no significant systemic toxicity	Moderate to strong (xenograft)	(32)
Nanoliposomes	Simvastatin	Patient-derived xenograft (PDX) mouse model (28-day treatment)	Reported as safe; tumor growth reduction not statistically significant; dose optimization and larger studies needed	Moderate/requires optimization	(33)

Metallic and magnetic nanoparticles offer additional advantages through targeted delivery and imaging capabilities. Green-synthesized silver nanoparticles exhibited acceptable biocompatibility and stability, while superparamagnetic iron oxide nanoparticles (SPIONs) enabled magnetically guided delivery and improved cellular uptake in preclinical models (36-39). SPIONs embedded in chitosan microspheres for uterine artery embolization were MRI-visible, allowing precise tracking of particle distribution and penetration into target tissues in rabbit models (40). These findings underscore the dual therapeutic and diagnostic potential of metallic nanocarriers.

Gene and RNA delivery platforms also demonstrated notable preclinical activity. Peptide-based nanoparticles functionalized with iRGD ligands significantly increased DNA transfection efficiency in fibroid cells, leading to persistent gene expression and targeted apoptosis with minimal effects on surrounding tissue (41, 42). Magnetic nanoparticle-based gene delivery enhanced transfer of suicide genes, demonstrating a bystander effect in adjacent fibroid cells (42). RNA-loaded lipid nanoparticles (RNA-LNPs) and CRISPR-based gene-editing platforms have shown potential for targeting key pathways such as MED12 mutations and TGF-β signaling, though most evidence remains in vitro or in preclinical models (43-52).

Combination approaches integrating nanotherapy with physical modalities such as HIFU or uterine artery embolization showed promising synergistic effects. Nanoparticles administered alongside HIFU enhanced local drug release, penetration, and therapeutic efficacy while minimizing systemic exposure (31, 32, 53). Similarly, SPION-chitosan microspheres demonstrated MRI-traceable embolization, suggesting potential for precise, minimally invasive, uterus-preserving interventions (40). These findings suggest that

integrating nanocarriers with non-surgical therapies could enhance treatment outcomes in fibroid management.

Table 2. Summary of Nano–Gene Therapy Strategies Discussed for Uterine Fibroids: Carrier Type, Cargo, Targeting Approach, and Biological Outcomes at the Cellular/Preclinical Level

Gene nanocarrier type	Genetic cargo	Targeting/ligand	Reported size	Method	Key reported outcomes	Reference
Peptide nanopolyplex (arginine–histidine-rich)	DNA	iRGD (targets integrin αvβ3)	~100–150 nm	Cellular / preclinical	Multi-fold increase in transfection efficiency; sustained gene expression; induction of apoptosis in target cells; no significant effect on adjacent healthy cells	(41, 42)
Spions + magnetofection	HSV-TK "suicide gene"	Magnetic-field guidance (physical targeting)	Not reported in the text	Preclinical	Marked increase in gene-transfer efficiency; bystander effect observed	(42)
Hybrid r6p-crgd + magnetic nanoparticles	Gene (exact type not specified in the text)	cRGD + magnetic field	Not reported in the text	Cellular / preclinical	Multi-fold enhancement of gene transfer; significant reduction in fibroid-cell proliferation	(41)
RNA-lnps (review / forward-looking)	RNA	Potentially improved with targeting ligands (e.g., αvβ3)	Not reported in the text	Review / preclinical	Potential platform for future personalized therapies; key challenges include RNA instability, innate immune responses, and difficulty crossing uterine tissue barriers	(43)

Emerging approaches, including ECM-targeted nanogels and local enzyme delivery systems, have demonstrated efficacy in reducing tissue stiffness and modulating fibrotic pathways. The combination of LiquoGel™ with Clostridium histolyticum collagenase (CCH) in ex vivo and in vivo studies reduced fibroid tissue stiffness and enhanced collagen degradation, with a first-in-human Phase I trial reporting approximately 39% reduction in collagen content and improvements in patient-reported pain without serious adverse events (54, 55). These studies highlight the potential of localized nanotherapy to specifically target fibroid ECM and fibroblast activity, offering a less invasive alternative to surgery.

Finally, exosomes and biosimilar nano-vesicles have been explored for their potential in diagnostics and targeted delivery. Fibroid-derived exosomes (HULM-EXO) were shown to modify endothelial cell activity, reorganize the tumor microenvironment, and stimulate proliferation and angiogenesis (56, 57). Although the clinical application of exosome-mediated drug delivery remains largely theoretical due to heterogeneity and standardization challenges, these findings suggest a promising avenue for non-invasive biomarker development and potential therapeutic delivery in the future.

In summary, preclinical evidence demonstrates that nanotherapeutic strategies—ranging from polymeric and liposomal carriers to magnetic, gene-based, ECM-targeted, and biosimilar nanoparticles—can achieve significant anti-fibroid effects, including tumor volume reduction, inhibition of cellular proliferation, induction of apoptosis, and modulation of ECM stiffness. Early clinical studies, primarily Phase I trials with ECM-targeting nanogels and HIFU integration, support safety and feasibility, although robust human data for most nanotherapy approaches remain limited.

Discussion

Nanotechnology presents a transformative potential for uterine fibroid (UF) management by enabling

uterus-sparing, minimally invasive treatments that could overcome limitations of conventional pharmacologic or surgical approaches. Polymeric and liposomal 2-methoxyestradiol (2-ME) platforms have demonstrated enhanced drug solubility, stability, and controlled release, improving therapeutic bioavailability while minimizing systemic toxicity. Similarly, gene and RNA nanocarriers offer precise modulation of molecular pathways implicated in fibroid pathogenesis, including aberrant growth signaling and extracellular matrix (ECM) remodeling. SPION-based systems enable dual diagnostic and therapeutic functions, allowing MRI-guided localization and targeted hyperthermia, while ECM-modulating injections, such as collagenase-loaded nanogels, facilitate localized degradation of fibrotic tissue, potentially improving tissue elasticity and symptom relief. The combination of these nanotherapeutic approaches with high-intensity focused ultrasound (HIFU) or other local delivery strategies further enhances treatment efficacy and safety, offering a synergistic approach to fibroid management.

Despite promising preclinical results, translation into human clinical practice faces significant challenges. Most evidence is derived from in vitro studies or animal models, and randomized clinical trials in humans remain scarce (31, 32, 58, 59). Biocompatibility and systemic clearance are major concerns, particularly for metallic or magnetic nanoparticles, which may accumulate in off-target organs, and for exosome-based carriers, where immunogenicity and reproducibility of vesicle preparations require further investigation (40, 60, 61). The dense ECM characteristic of fibroids may limit nanoparticle penetration, potentially necessitating higher doses, repeated administration, or ECM-targeted preconditioning to achieve adequate intertumoral delivery (8, 54). Furthermore, variability in nanoparticle composition, size, surface charge, and targeting moieties complicates standardization and cross-study comparison, making the identification of optimal design parameters challenging.

Emerging strategies, such as microenvironment-responsive nanoparticles, theranostic platforms combining therapy and imaging, and gene-editing nanocarriers, hold substantial promise by enabling precise, stimulus-responsive drug release and molecularly targeted interventions. However, these approaches require stringent preclinical validation, including assessment of off-target effects, immunogenicity, and long-term safety, before clinical translation can be realistically considered (62). Fertility outcomes following nanotherapy, particularly in combination with HIFU, remain inconsistent, with limited human data and variable reporting of ovarian reserve, endometrial function, and pregnancy rates (20, 63). Addressing these knowledge gaps through well-designed, controlled trials is essential to ensure both efficacy and reproductive safety.

In addition, patient-centered considerations, such as treatment tolerability, recovery time, and quality-of-life outcomes, must be integrated into translational research (64-66). Nanotherapy offers the potential to reduce hospitalization, avoid surgical morbidity, and preserve uterine integrity, which may be particularly relevant for women desiring future fertility. However, cost-effectiveness, regulatory approval pathways, and manufacturing scalability remain practical barriers that may influence the adoption of these technologies in routine clinical practice (67).

In summary, nanotechnology-based strategies represent a promising frontier in UF management, combining targeted molecular therapy, ECM modulation, and minimally invasive delivery approaches. While preclinical data are encouraging, robust human clinical trials and long-term safety studies are urgently needed to establish efficacy, reproducibility, and fertility outcomes. Future research should focus on optimizing nanoparticle design, improving delivery through dense fibrotic tissues, and integrating patient-centered endpoints to ensure safe and effective translation from bench to bedside (8, 54, 55).

Conclusion

Nanomedicine represents a transformative approach for the management of uterine fibroids, offering the potential for uterus-sparing, minimally invasive therapies. Preclinical studies highlight the efficacy of polymeric and liposomal drug platforms, gene and RNA nanocarriers, SPION-based systems, and ECM-modulating injections, particularly when combined with HIFU for targeted delivery. These strategies may improve therapeutic precision, reduce systemic toxicity, and preserve reproductive function.

Despite these promising advances, clinical translation remains limited by the scarcity of human trials, safety and biocompatibility concerns, and challenges in standardizing nanoparticle design and delivery. Future research should prioritize well-designed early-phase clinical trials, optimization of

nanoparticle targeting, biodistribution, and clearance, and evaluation of fertility-preserving outcomes. Consideration of cost-effectiveness, regulatory pathways, and health policy support will be essential to facilitate adoption, reduce the need for hysterectomy, and expand access to uterus-preserving care. Nanotechnology thus holds substantial promise to redefine fibroid management and improve quality of life for women seeking fertility-sparing treatment.

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Conflicts of Interest

The authors have no conflicts of interest to declare.

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